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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,548	03/15/2002	Jihoon Chang	58049-00002	6655

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JOSEPH HYOSUK KIM
JHK LAW
P .O. BOX 1078
LA CANADA, 91012-1078
CANADA

EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,548	CHANG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-3,5-16,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-19 are pending.

2. Applicant's election with traverse of Group IV, claims 4 and 17 drawn to a LK68 protein comprising amino acid sequence of human apolipoprotein(a) kringle domains IV36, IV37 and V38 in a serial manner and anticancer agent filed on 1/17/03, is acknowledged.

Upon reconsideration Examiner has rejoined Groups I-III with Groups IV to LK68 protein comprising amino acid sequence of human apolipoprotein(a) kringle domains IV36, IV37 and V38 and LK68 protein single Kringles domains, claims 1-4 and 17 read on the Groups rejoinder.

Applicant's traversal is on the grounds that the protein and nucleic acid claims should be joined and examined togother as they are linked by the special technical feature that the nucleic acid encodes the very proteins that are also claimed. Applicant further argues that the methods of using the various Kunitz-type domains such as protein or the nucleic acid are linked by the special technical feature of the agent effecting a treatment for an indicated condition. This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action. In addition, the different products such as proteins and nucleic acids are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Therefore, searching all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 5-16 and 18-19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-4 and 17 are under examination as they read on the LK68 protein comprising amino acid sequence of human apolipoprotein(a) kringle domains IV36, IV37 and V38 and LK68 protein single Kringles domains.

5. The references cited in the Search Report of PCT/KR99/00554 will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed and the cited references should be provided within the set period for reply to this Office Action.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The terms "amino acid sequences" and "kringle domains" in claims 1-3 are indefinite because human apolipoprotein(a) contains only one kringe IV36, one kringe IV37 and one kringeV38 domain that exists only once in the sequenced apo(a), while the claims indicate that the are more than one domain of IV36, IV37 and V38.

B. The phrase "serial manner" in claim 4, line 2, is indefinite, since serial indicates an arrangement in certain order. It is unclear which series or row order is been claimed.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition or LK68 of SEQ ID NO: 2, LK6 of SEQ ID NO: 4, LK7 of SEQ ID NO: 6 and LK8 of SEQ ID NO: 8 for inhibiting angiogenesis does not reasonably provide **enablement** for LK6, LK7 or LK8 protein "comprising: amino acid **sequences** of any IV36, IV37 or V38 **domains** respectively in claims 1-3 or any LK68 protein comprising amino acid sequences of human apolipoprotein(a) kringle **domains** IV36, IV37 and V38 in any "serial manner" in claim 4, any anticancer agent which comprises an active ingredient of LK68 protein, its "single kringles", or their "functional equivalents" and pharmaceutically acceptable carrier in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only SEQ ID NO: 2, 4, 6 and 8 with a disclosed activity of inhibiting anti-angiogenic activity (e.g., page 9 at lines 5-11). The instant claims encompass in their breadth *any* protein comprising multiple domains of IV36, IV37, V38 or any combination thereof; *any* "single kringles" or any "functional equivalents".

Applicant has not provided sufficient biochemical information that distinctly identifies such a protein comprising multiple kringles IV36, IV37 and/or V38 domains, functional equivalents, or protein comprising any multiple sequences of IV36, IV37 and V38 in any arrangement, other than those encompassed by the specific SEQ ID NO: 2, 4, 6 and 8.

The term "comprising " in claims 1-4 is open ended and extend the LK6, LK7, LK8 and LK68 to include additional amino acids other than SEQ ID NO: 4, 6, 8, and 2 respectively. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the inhibition angiogenesis that the relationship between the IV36, IV37 or V38 and its activity was not well understood. The specification is silent with respect to specifically which amino acids are critical to the claimed anti-angiogenic functions such that one skilled in the art could predict which species would fall within the scope of the claims to be used to inhibit angiogenesis. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. The reference demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

The state of the art does not appear to recognize the polypeptides of SEQ ID NO:2, 4, 6 and 8 would function in a method of inhibiting angiogenesis in a malignant condition. In an article (The Scientist 16:33, 2002, Learning from Angiogenesis Trial Failures) Fogarty M writes that 12 recent failures of Phase III angiogenesis trial failures have bashed some scientists' hopes for success. Furthermore, in the same article Claude Hariton indicates that "Multimodality is definitely the future in angiogenesis and antiangiogenic drug development because there is a dependency of several complex processes in angiogenesis. Shutting one door won't allow the drug to solve the problem. You have to shut, if possible, all the doors by which the vessels will grow around the tumor". Therefore, it is not clear that the skilled artisan could predict the efficacy of any "kringle domains" exemplified in the specification. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The current list of molecules identified as "anti-angiogenic" is extensive, with significant diversity in their structural, chemical and biological properties (see Fan et al., Trends in Pharm. Sci. 16(2):57-66, page 57, column 2 and page 65, column 1, first paragraph in particular).

Similarity, Wallace (Drug Discovery Today, 3(10):433-4) teach that while thee are ongoing clinical trials for the different categories of anti-angiogenic agents, we still have a limited understanding of the process of angiogenesis such that our ability to predict the efficacy of new agents is limited to the in vivo tumor growth animal models which often show promise in mice but are found ineffective in humans (page 433 column 2 in particular).

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-4 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a composition or LK68 of SEQ ID NO: 2, LK6 of SEQ ID NO: 4, LK7 of SEQ ID NO: 6 and LK8 of SEQ ID NO: 8 for inhibiting angiogenesis.

Applicant is not in possession of any LK6, LK7 or LK8 protein comprising amino acid sequences of IV36, IV37 or V38 kringles doamins respectively in claims 1-3 or any LK68 protein comprising amino acid sequences of human apolipoprotein(a) kringle domains IV36, IV37 and V38 in any serial manner in claim 4, any anticancer agent which comprises an active ingredient of LK68 protein, its single kringles, or their functional equivalents and pharmaceutically acceptable carrier in claim 17.

Applicant has disclosed only amino acid of SEQ ID NO: 2, 4, 6 and 8; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Cao et al (J Biol. Chem. 272:22924-22928, 1997).

Cao et al teach a kringle 5 (K5) of plasminogen, which is functional equivalent to the claimed kringles domains, is a novel inhibitor of endothelial cell growth. Cao et al further teaches that K5 is one of the most potent endogenous molecules for suppression of angiogenesis and tumor growth (see abstract and figure 1, page 22925, page 22928 last paragraph in particular). Cao et al teach human K5 in 20mM Tris buffer (see page 22925, 1st column 2nd paragraph in particular), which is considered to be a pharmaceutically acceptable carrier.

The reference teachings anticipate the claimed functional equivalents.

12. Claims 2 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Mikol *et al* (J Mol Biol. 256(4):751-61, 1996) (PTO-892 Ref. No. U, Paper No. 6).

Mikol *et al* teach a human apolipoprotein(a) (apo(a)) kringle type IV37 ($K4_{37}$) (see abstract and introduction page 751 in particular). Further, Mikol *et al* further teach the Apo(a) $K4_{37}$ in 80 mM NaCl which is also considered to be a pharmaceutically acceptable carrier (see page 759, under preparation of the crystals and data collection in particular).

While the prior art teachings may be silent as to the "anticancer agent" per se; the product in the reference is the same as the claimed product. Therefore "anticancer agent" is considered inherent property.

Since the office does not have a laboratory to test the reference IV37 kringle domain, it is applicant's burden to show that the reference IV37 kringle domain does not function as anticancer agent as recited in claim 17. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Applicant is reminded that when a claim recites using an old composition or structure (e.g. human apolipoprotein(a) kringle domins IV37) and the use is directed to a result or property of that composition or structure (anticancer), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Further, a composition is the same composition irrespective of its intended use.

The reference teachings anticipate the claimed invention.

13. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Kraft *et al* (Human Genetics. 95:275-282, 1995).

Kraft *et al* teach a human apolipoprotein(a) (apo(a)) kringle type IV37. The KIV37 has a single nucleotide exchange in the ultimate KIV37 of apo(a) at codon 4168 which results in an ATG (Meth) to ACG (Thr) substitution. Kraft et al teach that such substitution represents a common polymorphism. Finally, Kraft et al teach that the 4168 Met/Thr polymorphism has no effect on Lp(a) concentration, neither did it influence the lysine-binding property of the Lp(a) particle (see abstract and introduction page 275-276 and discussion page 280-281 in particular).

While the prior art teachings may be silent as to the "anticancer agent" per se; the product in the reference is the same as the claimed product. Therefore "anticancer agent" is considered inherent property.

The reference teachings anticipate the claimed invention.

14. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by McLean *et al* (Nature 33:132-137, 1987).

McLean *et al* teach a 4,548 protein sequence comprising amino acid sequence of human apolipoprotein(a) kringle domain IV36 at residues 4003-4093 (see sequence alignment and figure 1 and figure 5 in particular in particular). Mclean *et al* further teach that the 4,548 protein sequence comprising amino acid sequence of human apoliporotein(a) kringle domain IV37 at residues 4121-4209 (see sequence alignment and figure 1 and 5 on page 137 in particular). Furthermore, Mclean *et al* teach that the 4,548 protein sequence comprising amino acid sequence of human apoliporotein(a) kringle domain V38 at residues 4225-4310 (see sequence alignment in particular). Finally, Mclean *et al* teach that the 4,548 protein sequence comprising amino acid sequence of human apoliporotein(a) kringle domain IV36, IV37 and V38 at residues 4003-4310 (see sequence alignment in particular). The term "comprising" in instant claims 1-4 is open-ended, it would open up the claims to include the reference 4,548 amino acid sequence.

While the prior art teachings may be silent as to the "anticancer agent" per se; the product in the reference is the same as the claimed product. Therefore "anticancer agent" is considered inherent property.

The reference teachings anticipate the claimed invention.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claim 17 is rejected under 35 U.S.C. 103(a) as being obvious over McLean *et al* (Nature 33:132-137, 1987), in view of U.S Patent No. 6,413,963.

The teachings of McLean *et al* reference have been discussed, supra. McLean et al further teach that the lipoprotein(a) concentration in plasma is correlated with atherosclerosis (see abstract in particular).

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutically acceptable carrier.

The `963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound in a pharmaceutically acceptable carrier. (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the human apo(a) taught by Mclean *et al* reference in a pharmaceutically acceptable carrier taught by the `963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because apo(a) pharmaceutical compositions are used in a diagnosis of atherosclerosis factor as taught by Mclean et al reference.

Further, the claimed functional limitation would be inherent properties of the referenced composition. A composition is a composition irrespective of what its intended use.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
April 7, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600